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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,076	02/06/2004	Nicholas F. Landolfi	05882.0064.NPUS01	7347

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LEGAL DEPARTMENT
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EXAMINER	
KIM, YUNSOO	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,076	LANDOLFI ET AL.	
	Examiner	Art Unit	
	Yunsoo Kim	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,13-15,18,20-25,28,32 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,13-15,18,20-25,28,32 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/21/06 has been entered.

2. Applicant's amendment filed on 2/21/06 has been entered.
Claims 1, 10, 18 and 32 have been amended.
Claims 2, 11, 12, 16, 17, 19, 26-27, 29-31, 33-45 have been canceled.
Claims 46-49 have been added.
Claims 1, 3-10, 13-15, 18, 20-25, 28, 32, 46-49 are pending and are under consideration.

3. Applicant's IDS filed 2/21/06 has been acknowledged.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the CRF/Sequence Listing is missing mandatory numeric identifiers <150> and <151>, prior application and filing dates. In addition, numeric identifier <110> lists the applicant as "Landolfi et al." The <110> requires to list all the names of inventors preferably maximum of 10 names.

6. 35.U.S.C.101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 32 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, a product of nature. Claim 32 as written, does not sufficiently distinguish over a polypeptide as it exists naturally because the claim does not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3-10, 13-15, 18, 20-25, 28 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear whether the claimed chimeric antibody refers to an anti-amphiregulin antibody that specifically binds to SEQ ID NO:1 or anti-amphiregulin antibody that inhibits binding of the SEQ ID NO:1 and an anti-amphiregulin antibody.

Additionally, the limitation in claim 1, the heavy chain variable region having the amino acid sequence from the group consisting of SEQ ID NOs:2, 4, and 12 and the light chain variable region having the amino acid sequence from the group consisting of the SEQ ID NOs:3, 5 and 14, renders the claim indefinite as it is not clear whether it refers to the chimeric antibody or antibody that inhibits binding of the SEQ ID NO:1 and an anti-amphiregulin antibody.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 3-10, 13-15, 18, 20-25, 28, 32 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric or human antibody that competitively inhibits binding of an amphiregulin (AR) peptide to a receptor (see example 3) or an antibody specifically binds to a polypeptide consisting of SEQ ID NO:1 or antibody specifically binds to a polypeptide consisting of SEQ ID NO:1 wherein the antibody consisting of a heavy chain variable region consisting of SEQ ID NOs: 2, 4 or 12 and a light chain variable region consisting of SEQ ID NO: 3, 5, or 14 in presence of heavy and light constant regions, does not reasonably provide enablement for a chimeric or human antibody that competitively "inhibit binding of a amphiregulin polypeptide consist essentially of SEQ ID NO:1 to an anti-AR antibody", the antibody comprising at least 95% identical to the SEQ ID NO: 2, 3, 4, 5, 12, or 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficiently enabling description of the claimed invention.

There is insufficient guidance in the specification as filed as to how the skilled artisan would make and use the antibody and percent identical to sequences in the instant claims. A person of skill in the art would not know which amino acids are essential and which amino acids are non-essential, and what particular lengths identify essential polypeptides. There is insufficient guidance to direct a person of skill in the art to select any particular amino acid essential for antigen binding. The claim 18 as drafted is not limited to the given positions directed in p. 43 of the instant specification. Without detailed direction as to which fragment is essential to antigen binding, a person of skill in the art would not be able to determine which fragments are antigen binding without undue experimentation.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light

chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, of record, provided 3/11/05). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IFN-a antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

Furthermore, Applicant has no working examples demonstrating an antibody at least 95% identical to SEQ ID NOs:2, 3, 4, 5, 12, or 14 or any antibody binds to an AR peptide consists essentially of SEQ ID NO:1, given that the "consists essentially" considered opened for examining purpose.

In addition, the chimeric antibody that specifically binds to an AR polypeptide consisting of SEQ ID NO:1 does not inhibit binding of an amphiregulin polypeptide and an antibody comprising a heavy chain variable region from the group consisting of SEQ ID NOs:2, 4 and 12 and a light chain variable region from the group consisting of SEQ ID NOs: 3, 5 and 14. As evidenced in the instant specification, p. 3-4 overlapping paragraph, claim 10, p. 10, Fig. description, the claimed chimeric or humanized antibody is indeed PAR34, PAR80 or HuPAR34 described in SEQ ID NOs:2-5, 12 and 14, respectively. Thus, the identical antibody will not inhibit binding of an amphiregulin polypeptide to an anti-amphiregulin antibody.

Furthermore, Applicant has no working examples demonstrating a chimeric antibody inhibits binding of an amphiregulin to an antibody other than a receptor to an amphiregulin (see p. 39, ex. 3).

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breath of the claims, it would take undue trials and errors to practice the claimed invention.

12. Claims 1, 3-10, 13-15, 18, 20-25, 28, 32 and 46-49 are rejected under 35.U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a chimeric antibody to a polypeptide **consisting of** SEQ ID NO:1; and a chimeric antibody that consists of SEQ ID NOs: 2, 3, 4, 5, 12 or 14; however, applicant is not in possession of any antibody binds to an amphiregulin polypeptide **consists essentially of** SEQ ID NO:1, antibody at least 95% identical to the SEQ ID NO: 2, 3, 4, 5, 12, or 14 and antibodies having SEQ ID NO: 2, 3, 4, 5, 12, or 14

Given that "consists essentially of" considered open which includes non-disclosed amino acids to both ends, there are $1.1x\ 10^{26}$ possible combinations of amino acid sequences for addition of 10 amino acids to either ends of SEQ ID NO:1 alone without consideration of further combinations of antibodies at least 95% identical to SEQ ID NOs:2-5, 12 and 14.

There is insufficient written description to show that Applicant was in possession of an antibody encompassing "mutant", "polymorphic variant", "allelic variant" or "conservatively modified variant sequence" of the SEQ ID NO:1. The genus of the SEQ ID NO;1 encompasses a wide array of structurally and functionally distinct molecules. In contrast to the broad genus claimed, Applicant has failed to disclosed species other than SEQ ID NO:1. Therefore, Applicant does not possess the scope of claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use.

In addition, the instant claims are drawn to any antibody that shares at least 95% identity to SEQ ID NOs:2-5, 12 and 14 range 107-115 amino acid residues in length. There are $2.2x\ 10^{19}$ possible combinations of different antibodies that share at least 95% identity of SEQ ID NOs:2-5, 12 or 14. The instant specification does not describe any other antibodies than antibody consisting of the SEQ ID NOs:2-5, 12 and 14. Thus, the instant specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus of antibodies.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over the US Pat No. 5,830,995 in view of U.S.Pat No. 4,668,629.

The '995 patent teaches a monoclonal antibody to any epitope of AR polypeptide (see SEQ ID NO:7), the antibody fragments, (col. 15, lines 43-51), increased AR expression in tumor cells (col. 13, lines 45-56), blocks cell growth (col. 14, lines 38-49), neutralizing activity (col. 13, lines 57-60), conjugation to effector moiety for labeling (col. 24, lines 40-65) and competition of ligand binding (col. 31, lines 49-67).

The claimed invention differs from the reference teachings only by the recitation of human antibody.

However, the '629 patent teaches how to make human monoclonal antibodies and the advantages of using human monoclonal antibodies in therapy as human monoclonal antibodies are less immunogenic (col. 4, lines 51-64).

It would have been obvious to one of the ordinary skill in the art at the time the inventions was made to employ the human monoclonal antibodies taught by the '629 patent in the monoclonal antibody to treat psoriasis taught by the '995 patent to make the therapy more attainable and effective by having less immunogenic human monoclonal antibody.

One of the ordinary skill in the art at the time the invention was made would have been motivated to do so because the teachings of Kaplan et al. is an obvious way to improve the therapy more effective and less immunogenic as in the claimed invention. Thus, it is expected to combine teachings above to enhance the atherosclerosis therapy as in claimed invention.

From the combined teachings of references, one of ordinary skill in art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary skill in the art at the time the invention was made, as evidenced by references, especially in the absence of evidence to the contrary.

15. No claim is allowed.
SEQ ID NOs:2, 3, 4, 5, 12 and 14 are free of art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/12/06

Yunsoo Kim
Patent Examiner
Technology Center 1600
May 3, 2006

Gerald R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600

Notice to Comply	Application No. 10/774,076	Applicant(s) Landolfi et al.	
	Examiner KIM	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Numeric identifiers <150> and <151> are missing and <110>is incorrect.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
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